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No. 06-1249

In the Supreme Court of the United States

WYETH,
Petitioner,
v.

DIANA LEVINE,
Respondent.

On Writ of Certiorari to the Vermont Supreme Court

BRIEF OF THE CALIFORNIA MEDICAL ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENT

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INTEREST OF *AMICUS CURIAE*[1]

The California Medical Association ["CMA"] is a nonprofit, incorporated professional association of more than 35,000 physicians who are engaged in the private practice of medicine, in all specialties and modes of practice, in the State of California. Its mission is to promote the science and art of medicine, the care and well-being of patients, the protection of the public health, and the betterment of the medical profession.

CMA and the thousands of physicians and patients it represents have as their highest priority insuring that patients receive the best medical care possible. For that reason, CMA and its members diligently monitor and carefully consider the consequences to patients of important public policy issues such as preemption of pharmaceutical failure-to-warn claims.

Because preemption of pharmaceutical failure-to-warn claims would obstruct physicians' access to complete and truthful information about prescription drug safety and efficacy and force doctors to try to uncover such information on their own, it would compromise patient safety. Preemption would then

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[1] Each party has consented to the filing of this brief. The parties' letters of consent are filed with the Court. No counsel for a party authored in whole or in part, and no party or their counsel made a monetary contribution intended to fund the preparation or submission of this brief.

leave these patients without recourse for drug-related injuries and put physicians at risk by potentially allowing drug manufacturers to shift liability for such injuries to doctors. The unfounded fear of "overwarning,"[2] cannot justify placing patients and doctors at risk.

To protect patient safety, *Amicus,* the California Medical Association, files this brief in support of Respondent Diana Levine on its own behalf and on behalf of its members' patients who will be directly and adversely affected by preemption.

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[2] As used by Petitioner and its *amici*, "overwarning" is loosely defined as including allegedly trivial and scientifically-unjustified information in prescription drug labels. *See, e.g.*, Brief of Pharmaceutical Research and Manufacturers of America and Biotechnology Industry Organization as *Amici* Curiae Supporting Petitioner (Wyeth) [hereafter "PhRMA/BIO Brief"], at 15.

SUMMARY OF ARGUMENT

Physicians serve their patients best when they have access to complete and truthful information about the risks and benefits of the drugs they prescribe. Without it, they cannot properly evaluate the complex interaction between a prescription drug and a patient's unique body chemistry.

Because preempting failure-to-warn claims would make the U.S. Food and Drug Administration ["FDA"] approval the final word on a drug's safety, it would significantly weaken manufacturers' incentives to conduct new safety studies, to monitor their drugs in the marketplace, to improve them post-approval, and to supply FDA and doctors with new or revised safety information. Moreover, it would deprive physicians of the important drug safety information that has unfortunately come to light only in failure-to-warn litigation. In the absence of viable alternative sources for this information, physicians would be unable to provide patients with the best possible care and patient safety would be at risk.

Preempting failure-to-warn claims would also put doctors at risk. First, it may subject them to new and unwarranted liability for the consequences of drug defects and potentially shift financial responsibility for injuries to physicians and patients. In doing so, it may rob physicians of their ability to challenge the adequacy of drug warnings in defense of such claims. This potential for new liability would undermine long-standing efforts to protect doctors from suit and could well drive some physicians from the profession.

Moreover, preemption of failure-to-warn claims may also require that physicians become one-man FDA's as they attempt to uncover hidden or unclear safety risks to protect their patients. This search would add unduly to the considerable time and financial pressures practicing physicians already face.

These demonstrable harms vastly outweigh the absence of any actual risk of alleged "overwarning." Neither Petitioner nor its *amici* has provided this Court with a single instance in which tort litigation has actually forced a word or phrase to be included in any prescription drug label. Instead, they describe public panics, misinformation in the public domain, or so-called "black box" warnings that contain life-threatening, verified risks. Preemption, however, would eliminate none of these things.

Since they have not shown that "overwarning" even exists in this context, Wyeth's *amici* have not demonstrated that alleged "overwarning" has led to underuse of prescription drugs. It is not surprising then that neither Petitioner nor its *amici* have produced a single example of any actual connection between the two, if any exists.

Because preemption is unwarranted and would needlessly put physicians and patients alike at risk, the undersigned *amici* ask that the decision of the Vermont Supreme Court be affirmed.

ARGUMENT

I. By Making FDA Approval the Last Word on a Drug's Safety, Preemption of Failure-to-Warn Claims Would Jeopardize Patient Safety

A. Physicians Require Full and Accurate Information About Drug Safety to Treat Their Patients Safely

The Hippocratic oath mandates that physicians "prescribe regimens for the good of [their] patients according to [their] ability and judgment and never do harm to anyone" or knowingly "prescribe a deadly drug."[3] To satisfy its requirements,

> [Physicians must have access to all relevant medical information regarding . . . various medications that we discuss with and recommend to our patients. Any obstacle placed in the way of full and complete communication with our patients undermines the trust upon which the doctor-patient relationship is

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[3] LEWIS RICHARD FARNELL, THE CULT OF ASKLEPIOS, 269-70 (Oxford: Clarendon Press) (1921).

> based and prevents us from providing the best care we can to our patients.[4]

Treating physicians can provide the best possible care only when they have fullest possible access to the widest available array of truthful information. When examining and treating patients, physicians review the patient's medical history and whatever reliable information is available about a needed drug. FDA acknowledges that it plays only a supporting role in patient care and that "it is essential to the safe use of a drug for the physician to know all adverse reactions that are likely to occur with it."[5] FDA "believes that practicing physicians will welcome such information so that they can make their best informed medical judgments in the care of their patients."[6]

To that end, FDA regulations require that manufacturers include in prescription drug labeling all "[i]nformation that would ***affect decisions about***

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[4] Press Release, Barry B. Perlman, President, New York State Psychiatric Association (June 2, 2004), http://www.oag.state.ny.us/press/2004/jun/jun2b_04_ attach2.pdf.

[5] Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434, 37,443 (June 26, 1979).

[6] *Id.* at 37,447.

whether to prescribe a drug,"[7] including "a list of the most frequently occurring adverse reactions."[8] Medical journal boards and FDA have recognized, however, that drug manufacturers sometimes fail to disclose critical safety information about substantial health hazards or misrepresent such facts to doctors. For example, both *The Lancet*[9] and *New England Journal of Medicine* ["NEJM"][10] have harshly criticized Merck for allegedly misleading or failing to disclose to the medical community data regarding cardiovascular risks associated with its arthritis drug Vioxx that both deemed important to patient safety. Similarly, FDA itself is investigating whether Eli Lilly submitted false or misleading data concerning diabetic side effects of its anti-psychotic drug Zyprexa in its promotional materials and sales pitches to doctors.[11]

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[7] 21 C.F.R. § 201.57(a)(10) (2008) (emphasis supplied).

[8] 21 C.F.R. § 201.57(a)(11) (2008).

[9] Richard Horton, Commentary, *Vioxx, the Implosion of Merck, Aftershocks at the FDA*, 364 THE LANCET 1995 (2004).

[10] Gregory D. Curfman et al., Editorial, *Expression of Concern Reaffirmed,* 354 NEW ENG. J. MED. 1193 (2006); Gregory D. Curfman et al., *Expression of Concern: Bombardier et al., Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*, 343 NEW ENG. J. MED. 1520 (2000), 353 NEW ENG. J. MED. 2813 (2005).

[11] Alex Berenson, *U.S. Wonders If Zyprexa Drug Data Was Accurate*, N.Y. TIMES, Apr. 25, 2007, at C1; *see also* Thomas O.

FDA lacks the tools and resources to uncover and to provide physicians with this kind of information on its own. The Food Drug and Cosmetic Act ["FDCA"] neither grants FDA subpoena power nor does its limited information-gathering authority extend to documents reflecting internal deliberations over safety hazards or analyses of drug performance.[12] Instead, FDA takes what it gets from drug companies. In fact, "as often as not, the information that agencies do obtain on underlying malfeasance by regulatees comes to them indirectly through tort litigation."[13] These limitations call into question the legitimacy and value to physicians of FDA decisions about prescription drugs. "To the extent that regulatory agencies cannot generate the information they need for accurate

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McGarity, *The Complementary Roles of Common Law Courts and Federal Agencies in Producing and Using Policy-Relevant Scientific Information*, 37 ENVTL. L. 1027, 1051 (Fall 2007); *and* Alex Berenson, *Eli Lilly Said to Play Down Risk of Top Pill*, N.Y. TIMES, Dec. 17, 2006, at A1.

[12] *See* 21 U.S.C. § 355(k) (2008); *and* David C. Vladeck, *Defending Courts: A Brief Rejoinder to Professors Fried and Rosenberg*, 31 SETON HALL L. REV. 631, 633-35 (2001).

[13] THOMAS O. MCGARITY, THE PREEMPTION WAR 204 (Yale Univ. Press 2008) (citing Aaron S. Kesselheim et al., *The Role of Litigation in Defining Drug Risks*, 297 JAMA 308 (2007)).

decision-making, the advantage in technical expertise that they have over the courts is largely lost."[14]

For these reasons, the medical community has recognized that FDA approval does not and cannot assure drug safety nor guarantee that doctors receive the information they need to prescribe drugs safely.[15] The National Academy of Sciences' Institute of Medicine found that deficiencies in FDA's drug safety system directly impacted the quality of risk information provided to physicians.[16] A recent *Journal of the American Medical Association* ["JAMA"] editorial against preemption of failure-to-warn claims explained:

> Curbing frivolous lawsuits is a worthy goal, but limiting legal involvement in the prescription drug arena is likely to

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[14] *Id.* (citing Wendy Wagner, *Stubborn Information Problems and the Regulatory Benefits of Gun Litigation in* SUING THE GUN INDUSTRY 225, 231, 271 (Timothy D. Lytton ed., Univ. of Mich. Press 2005)).

[15] Lawrence O. Gostin, *The Deregulatory Effects of Preempting Tort Litigation: FDA Regulation of Medical Devices*, 299 JAMA 2313, 2314 (2008).

[16] COMM. ON THE ASSESSMENT OF THE U.S. DRUG SAFETY SYS., THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC 4 (Alina Baciu et al. eds., Nat'l Acad. Press 2007), *available at* http://www.nap.edu/catalog.php?record_id=11750.

> increase the nation's problem of poorly defined or inadequately presented drug risk information. These case studies indicate that clinical trials and routine regulatory oversight as currently practiced often fail to uncover important adverse effects for widely marketed products. In each instance, the litigation process revealed new data on the incidence of adverse events, enabled reassessments of drug risks through better evaluation of data, and influenced corporate and regulatory behavior. In performing these tasks, lawyers and their clients often find themselves serving as drug safety researchers of last resort.[17]

While *amici* do not necessarily believe that the tort system is the most efficient tool to insure drug safety, "[r]ecent history casts some doubt on the ability of FDA alone to protect the public and, thus, on the wisdom of dispensing with tort law."[18]

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[17] Kesselheim et al., *supra* note 13, at 308-311.

[18] Russell Korobkin, *Who Should Protect the Public? The Supreme Court and Medical Device Regulation*, 357 NEW ENG. J. MED. 1680, 1681 (2007); *see also Bates v. Dow AgroSciences, LLC,* 544 U.S. 431, 451 (2005) (Breyer, J., dissenting) ("tort suits can serve as a catalyst" to aid "in the exposure of new dangers and their consequences").

B. Preemption Would Stop the Flow to Doctors of Critical Drug Safety Information

Preemption of pharmaceutical failure-to-warn claims would obstruct the flow of drug safety information to doctors in several ways. First, it would seriously diminish the drug industry's incentive to disclose safety information to FDA and, through it, to doctors, or to alter its labels to reflect new drug hazards.[19] As one recent commentator explained:

> If courts extended federal preemption to drug claims . . . manufacturers would have little incentive to conduct post-approval clinical studies to examine a drug's safety. The FDA also would lose one of its few bargaining chips in pressuring companies to amend labels to warn of newly discovered risks. If failure-to-warn claims were not actionable, drug companies could effectively resist all efforts by the FDA to expand warnings.[20]

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[19] *Bates,* 544 U.S. at 450.

[20] Jonathan V. O'Steen, *The FDA Defense: Vioxx and the Argument Against Federal Preemption of State Claims for Injuries Resulting From Defective Drugs,* 48 ARIZ. L. REV. 67, 95 (Spring 2006).

In short, preemption would give drug manufacturers "a free pass to avoid making the otherwise statutorily required label changes with no simultaneous, conscious purpose to enhance safety or availability."[21] Drug manufacturers who have, or could, obtain information about increased risk that would otherwise have to be disclosed would be protected from the consequences of their failure to disclose.

This is true even if one believes that FDA has superior expertise in determining drug warnings' contents. Although FDA has historically faced mountains of information about products it regulates, it is not always able to process such information in a timely fashion.

> [T]he FDA can rely on the incentives of the tort system to encourage manufacturers to continue research, reveal research results honestly, monitor scientific literature, and request or issue appropriate warnings. Preemption would remove those incentives, and it is unclear whether the FDA could adequately review drug information under its current

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[21] Mary J. Davis, *The Battle Over Implied Preemption: Products Liability and the FDA,* 48 B.C. L. REV. 1089, 1143 (2007).

> staffing and budget without the support of private lawsuits.[22]

As demonstrated above, in addition to diminishing manufacturer incentives, preemption of failure-to-warn claims would also significantly reduce or potentially end doctors' access to drug safety information that comes to light in tort litigation.[23] While physicians do not support unfounded lawsuits, in the absence of alternative sources for such information, they must continue to rely on meritorious lawsuits to reveal significant threats to patient safety.

In recognition of these dangers, major medical journals have strongly opposed preemption because the alleged benefits of providing absolute immunity to drug manufacturers through preemption are far outweighed by the harm to patient care and physicians.[24] It would be a disservice if those most responsible for drug safety enjoyed the protections of preemption while health care

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[22] Howard A. Denemark, *Improving Litigation Against Drug Manufacturers for Failure to Warn Against Possible Side Effects: Keeping Dubious Lawsuits from Driving Good Drugs Off the Market,* 40 CASE W. RES. L. REV. 413, 431 (1990).

[23] Richard A. Nagareda, *FDA Preemption: When Tort Law Meets the Administrative State*, 1 J. TORT L. 1, 45 (2006), *available at* http://www.bepress.com/jtl/vol1/iss1/art4.

[24] *See, e.g.,* Leonard M. Glantz et al., *The FDA, Preemption, and the Supreme Court,* 358 NEW ENG. J. MED. 1883 (2008); Gostin, *supra* note 15, at 2313.

providers and patients were left to suffer the consequences of their drugs' failures and defects alone.

II. Preemption of Failure-To-Warn Claims Would Put Physicians at Risk

A. Preemption May Subject Physicians to New and Unwarranted Liability

It is unlikely that preemption of failure-to-warn claims would immunize doctors from malpractice claims alleging improper drug prescription.[25] While the preamble to 2006 FDA regulations[26] implies that failure-to-warn claims against providers are

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[25] Only a few cases address preemption's impact on malpractice claims and all find that such claims are not preempted. *Nealy v. U.S. Healthcare HMO*, 711 N.E.2d 621, 622 (N.Y. 1999) (ERISA); *Brooks v. Maryland Gen. Hosp., Inc.*, 996 F.2d 708, 714 (4th Cir. 1993) (no preemption of state malpractice law under EMTALA); *Aragon v. Federated Dep't Stores, Inc.*, 750 F.2d 1447 (9th Cir.), *cert. denied*, 474 U.S. 902 (1985) (malpractice claim against attorneys provided by union not preempted); *Evitt v. University Heights Hospital,* 727 F. Supp. 495, 498 (S.D. Ind. 1989) (medical malpractice claim not preempted by COBRA); *see also New York State Conf. of Blue Cross & Blue Shield Plans v. Travelers Ins. Co.*, 514 U.S. 645, 658-68 (1995) (addressing applicability of COBRA to physicians claims); *Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 715 (1985).

[26] *See* Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3933 (Jan. 24, 2006) (effective June 30, 2006) (codified at 21 C.F.R. § 201, 314, 601).

preempted, it does not specifically address malpractice claims. *Id.* In fact, Petitioner argued below that Diana Levine's injuries resulted from her physicians' negligence and did not argue that her claims against her doctors were preempted.[27] Moreover, at a recent hearing on preemption of their claims against manufacturers, Senator Orrin Hatch suggested that the women injured by prescription drugs and medical devices who testified sue their doctors instead.[28]

Most states' laws do not permit FDA approval to render prescription drug warnings adequate as a matter of law.[29] In defending against malpractice claims based upon alleged negligence in prescribing drugs for a patient, doctors may, therefore, question the adequacy of their warnings.

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[27] *See, e.g.,* Brief of Petitioner Wyeth at 19-20; Brief of Respondent Diana Levine at 17-19.

[28] *Short-Change for Consumers and Short-Shrift for Congress?, The Supreme Court's Treatment of Laws That Protect American's Health, Safety, Jobs and Retirement Hearing Before the Senate Judiciary Committee*, 110th Cong. 2nd Sess. (2008) (Statement of Sen. Orrin Hatch), *available at* http://judiciary.senate.gov/ hearing. cfm?id= 3404.

[29] *See, e.g., Estate of Montagne v. Bristol-Myers Squibb,* 111 P.3d 857 (Wash. App. 2005); *Edwards v. Basel Pharm.,* 933 P.2d 298 (Okla. 1997); *MacDonald v. Ortho Pharm. Corp.,* 475 N.E.2d 65 (Mass.), *cert. denied,* 474 U.S. 920 (1985).

By effectively decreeing that FDA-approved warnings, no matter how opaque, are adequate as a matter of law and charging doctors with knowledge of their contents and meaning, however, preemption may subject doctors to unwarranted medical negligence claims. As the result, physicians would run a significant risk of suit and liability based on the assumption that FDA-approved labels are clear when, in fact, they are not.

Thus, preemption of failure-to-warn claims threatens to shift liability for adverse drug side effects to physicians, undermining decades-long efforts to protect them from tort suits,[30] and to facilitate the drug industry's off-loading financial responsibility for such injuries to doctors and their patients. Such a shift may even force some doctors to abandon their practices.

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[30] *See* Cal. Civ. Code § 3333.2 (West 2007) (limits non-economic damages in suits against health care providers); FLA. STAT. Ch. 768.28 (2008) (recovery limits); FLA. STAT. Ch. 768.73 (2008) (limits punitive damages); TEX. CONST. art. III § 66 (limits non-economic damages in lawsuits against health care providers); TEX. CIV. PRAC. & REM. CODE ANN. § 74.301 (Vernon 2008) (limits non-economic damages); TEX. CIV. PRAC. & REM. CODE ANN. § 41.008 (Vernon 2007) (limits recovery of punitive damages).

B. Preemption Would Place Undue Pressure on Physicians to Uncover Drug Safety Information Independently

It is no secret that physicians face increasing time and financial pressures. In one survey, 75% of the doctors with managed care contracts said they felt pressured to see more patients.[31] Twenty-eight percent "reported that they felt pressure to limit what they told patients about treatment options," 57% felt pressured to restrict their referrals, and nearly a third of these doctors said the pressure was severe enough to compromise the quality of care. *Id.*

Physicians must also deal with an increasing barrage of potentially misleading information about prescription drugs. Physicians perceive that "Internet information often generate[s] patient misinformation, leading to confusion, distress, or an inclination towards detrimental self-diagnosis and/or self-treatment. Physicians felt these influences added a new interpretive role to their clinical responsibilities."[32]

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[31] Kevin Grumbach et al., *Primary Care Physicians' Experience of Financial Incentives in Managed Care Systems*, 339 NEW ENG. J. MED. 1516 (1998).

[32] Farah Ahmad et al., *Are Physicians Ready for Patients With Internet-Based Health Information?*, 8 J. MED. INTERNET RES. e22 (2006), http://www.pubmedcentral.nih.gov/article render.fcgi?artid =2018833.

Industry-generated direct-to-consumer advertising also pressures doctors to explain drug claims and prescribe requested but unwarranted drugs. This Court has acknowledged that pressure.[33] Doctors may also soon be faced with additional scientific studies on unapproved, commonly referred to as "off-label," drug uses if proposed regulations allowing companies to send doctors such information are promulgated.[34] The medical community has recognized, however that, while "[p]eople are viewing reprints as science and they believe that science is objective . . . industry uses research to advance marketing goals."[35]

At the same time, FDA is no longer capable of ensuring that medical professionals receive all relevant information about the risks of prescription medications. In addition to studies previously cited, a 2006 Government Accountability Office report expressed grave concerns about FDA's ability to

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[33] *Thompson v. Western States Medical Center, et al.,* 535 U.S. 357, 378 (2002) (Breyer, J., dissenting).

[34] Draft Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Article and Medical or Scientific Reference Publication on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices, 73 Fed. Reg. 9342 (Feb. 20, 2008).

[35] Mike Mitka, *Critics Say FDA's Off-Label Guidance Allows Marketing Disguised as Science,* 299 JAMA 1759 (2008).

monitor the safety of approved drugs.[36] Last year, a subcommittee of FDA's own Science Board "concluded that science at the FDA is in a precarious position: the Agency suffers from serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities."[37] "FDA's inability to keep up with scientific advances," the report explained, "means that American lives are at risk." *Id.* at 3.

Were this Court to preempt failure-to-warn claims, it would reduce significantly the incentive for drug companies to supply doctors and FDA with critical safety information and cut off information generated in pharmaceutical litigation. Without access to such reliable sources of information about a drug's adverse side effects, physicians may have to become "drug safety researchers of last resort"[38] as they attempt to uncover safety information on their own. With little or no help from FDA, none from the courts, with drug companies actively promoting drug benefits

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[36] U.S. GOV'T ACCOUNTABILITY OFFICE, DRUG SAFETY: IMPROVEMENT NEEDED IN FDA'S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS 5 (2006), *available at* www.gao.gov/cgi-bin/getrpt?GAO-06-402.

[37] U.S. FOOD & DRUG ADMINISTRATION, REPORT OF THE SUBCOMMITTEE ON SCIENCE AND TECHNOLOGY, FDA SCIENCE AND MISSION AT RISK 2 (2007), *available at* http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20 Technology.pdf.

[38] Kesselheim et al., *supra* note 13, at 308-311.

but lacking incentive to disclose risks, and with patients increasingly armed with direct-to-consumer advertising and Internet health information, it will become increasingly difficult for physicians to obtain the full and accurate information they must have to treat their patients safely. Consequently, patient safety will suffer and the financial responsibility for that suffering will be disproportionately and unfairly borne by physicians and their patients.

III. Alleged "Overwarning" Does Not Justify Preemption of Failure-to-Warn Claims

Against the backdrop of major drug litigation, it is telling that the drug industry has not provided this Court with a single unwarranted word or phrase ever actually included in any prescription drug label as its result, let alone showed the "proliferation of inappropriate warnings" in FDA-approved labels one *amicus* claims.[39] In the many briefs the industry filed, there is not one example of a failure-to-warn suits' actually causing any manufacturer to include "virtually all known adverse event information, regardless of its importance" in its label.[40] In fact, numerous courts

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[39] *See* PhRMA/BIO Brief at 15. Even FDA's recent discussion of overwarning is entirely theoretical. *See* Requirements on Content and Form of Labeling for Human Prescription Drug and Biological Products, *supra* note 26, at 3935.

[40] *See* PhRMA/BIO Brief at 15.

have rejected the industry's overwarning arguments simply because of the absence of any factual support for them.[41]

The risk to Diana Levine of gangrene or lost limbs from the administration of Phenergan through IV-push injection is hardly insubstantial or speculative. The same is true of FDA-ordered "black-box" suicide warnings now present in the labels of certain anti-depressants.[42] Moreover, where, as here, the issue is not whether a drug should have been used at all but which of several methods of administration should have been employed, the alleged dangers of overwarning – removal of the drug from the market and under-use – are not implicated because the patient would have received the drug either way.

More important, it is impossible to overwarn in the prescription drug context because manufacturers are already obligated by law to include in their labels anything that would affect a physician's decision to prescribe a drug, including recurring adverse events.[43] If information is too trivial or speculative even to

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[41] *See Cartwright v. Pfizer, Inc.,* 369 F. Supp. 2d 876, 886 (E.D. Tex. 2005); *Witczak v. Pfizer, Inc.*, 377 F. Supp. 2d 726, 732 (D. Minn. 2005); *Zikis v. Pfizer*, 2005 WL 3019409 at *4 (N.D. Ill. May 9, 2005); *see also Colacicco v. Apotex, Inc.,* 521 F.3d 253, 277 (3d Cir. 2008) (Ambro, J., dissenting).

[42] *See* PhRMA/BIO Brief at 17.

[43] 21 C.F.R. § 201.57(a)(10), (11) (2008).

change a prescribing decision, its disclosure poses no risk of under-treatment or drug under-utilization sufficient to drive a drug from the market.

There is likewise little actual danger that including allegedly trivial or unsubstantiated information in a drug label would so thoroughly confuse doctors about real dangers that they would be too confused to utilize a drug properly. Justice Breyer noted that "doctors . . . obtain information about individual drugs through many other channels" and are nevertheless able to filter through it.[44] Even with a barrage of Internet health information and direct-to-consumer advertising, physicians have been able to separate reliable information and sources from unreliable ones. Thus, including a little additional information in a prescription drug label is unlikely to flummox completely trained physicians.

Moreover, the drug industry has not expressed any concern about confusing or overwhelming doctors in asserting an alleged constitutional right to send doctors industry-sponsored[45] scientific papers on potential drug benefits, including unapproved off-label

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[44] *Thompson,* 535 U.S. at 378 (Breyer, J., dissenting).

[45] Barton Moffatt et al., *Ghost Marketing: Pharmaceutical Companies and Ghostwritten Journal Articles*, 50 PERSPECTIVES BIOL. MEDICINE 18 (2007).

uses.[46] They have also lobbied FDA for proposed rules to allow immediate dissemination of such materials.[47]

Apparently, overwarning has become an issue for drug companies only as they have tried to promote directly to the public prescription drugs containing warnings written for physicians. In fact, *amici* mistakenly argue that "***patients*** [not doctors] may be deterred from using a needed medicine in the face of intimidating warnings . . ."[48] The alleged examples they discuss do not involve prescription drug labels and, therefore, provide no support for the notion that ***doctors*** have been overwarned.[49] Preemption of failure-to-warn claims will not stop Internet rumors, public panics, or patient non-compliance. Instead, doctors armed with complete and accurate information are the best defense against patient confusion.

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[46] *See, e.g.,* Daniel E. Troy et al, *Pharmaceutical Promotion and First Amendment Rights,* 359 NEW ENG. J. MED. 536, 536-37 (2008).

[47] Draft Guidance for Industry on Good Reprint Practices, *supra* note 34, at 9342.

[48] PhRMA/BIO Brief at 14 (emphasis supplied).

[49] *Id.* at 16-25; Brief of *Amici* Washington Legal Foundation ["WLF"] and American College of Emergency Physicians ["ACEP"] as *Amici* Curiae in Support of Petitioner (Wyeth) [hereafter "WLF/ACEP Brief "], at 16-26.

A. Wyeth's *Amici* Have Not Demonstrated that "Overwarning" in Prescription Drug Labels Exists

Although Wyeth's *amici* attempt to provide examples of overwarning to justify preempting failure-to-warn claims, they fail in that attempt. Several illustrations do not even involve prescription drugs. Only one concerns anything contained in a prescription drug label but addresses risks that FDA itself had already determined were life-threatening and scientifically-warranted. As such, including these risks in a drug's label can hardly be classified as "overwarning." To the extent any of these anecdotes addresses tort lawsuits, it is to blame tort claims on alleged "overwarning" rather than argue, as industry *amici* do, that the lawsuits caused manufacturers to overwarn. Thus, these anecdotes do not demonstrate that alleged overwarning in prescription drug labels as the alleged result of tort claims, if it occurs at all, is so severe as to warrant preempting failure-to-warn claims.

Teen Suicide and SSRI's[50]

Several industry *amici* suggest that the pediatric suicide warnings issued as early as 2003 for certain anti-depressants actually led to an increase in teen suicides in 2003-05 in the U.S. and Europe.[51] The idea that information contained in a so-called "black box" can be considered as "overwarning" has no merit. Only FDA can order a black-box warning.[52] Moreover, black-box warnings are ordered only for what the FDA deems as the most serious, scientifically-justified risks, hardly candidates for the term "overwarning."[53]

Second, these warnings pertain to a mostly unapproved use of these drugs and are, therefore, irrelevant to preemption which makes FDA approval sacrosanct. Despite widespread off-label use, only one

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[50] So-called SSRI's are a class of anti-depressants known as selective serotonin reuptake inhibitors.

[51] Robert D. Gibbons et al., *Early Evidence on the Effects of Regulators' Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents*, 164 AM. J. PSYCHIATRY 1356, 1361-62 (2007); *see also* WLF/ACEP Brief at 17, PhRMA/BIO Brief at 17-18.

[52] Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434, 37,448 (June 26, 1979).

[53] *See* 21 C.F.R. § 201.57(c)(1) (2008).

of the anti-depressants studied – Prozac – has ever been approved for pediatric use in the United States.[54]

Viewed in their proper light then, pediatric suicide warnings might have provided an illustration of what happens when a medically-verified warning regarding a very serious risk of an off-label use is issued. It is unfortunate that they cannot offer even that modest contribution because the study was limited to "early evidence,"[55] and its conclusions have not been confirmed by more complete and final data.

When statistics for suicide rates for 2005 became available, they revealed that fewer people under 25 committed suicide in 2005 than in 2004 when the black-box suicide warning was ordered.[56] Recent studies conducted in Great Britain confirm that reductions in anti-depressant prescriptions after

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[54] NATIONAL INST. OF MENTAL HEALTH, ANTI-DEPRESSANT MEDICATIONS FOR CHILDREN AND ADOLESCENTS: INFORMATION FOR PARENTS AND CAREGIVERS, *available at* http://www.nimh.nih.gov/health/topics/child-and-adolescent-mental-health/anti-depressant-medications-for-children-and-adolescents-information-for-parents-and-caregivers.shtml (last visited Aug. 12, 2008).

[55] Gibbons, *supra* note 53, at 1356.

[56] HSIANG-CHING KUNG ET AL., DEATHS: PRELIMINARY DATA FOR 2005, CENTERS FOR DISEASE CONTROL, NATIONAL CENTER FOR HEALTH STATISTICS, *available at* http://www.cdc.gov/nchs/products/pubs/pubd/hestats/prelimdeaths05/prelimdeaths05.htm (last visited Aug. 12, 2008).

enhanced suicide warnings were issued did not lead to an increase in child and adolescent suicides.[57] Moreover, while Gibbons purports to show an association between a spike in suicides in 2003 and 2004 and alleged reductions in prescriptions for SSRI's, his own data reveals that there was virtually no reduction in prescriptions for the drugs studied during that period.[58] Instead, the reductions began in 2004, the year FDA ordered the black-box warning. *Id.*

Fish and Pregnancy

Fish is not a prescription drug. It has no warning label and does not need FDA approval or a doctor's prescription before it can be served to any willing diner *en papillote.* Likewise, *What to Expect When You are Expecting*[59] is not a peer-reviewed scientific journal usually relied upon by practitioners for medical information. Third, food contamination has

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[57] Benedict W. Wheeler et al., *The Population Impact on Incidence of Suicide and Non-fatal Self Harm of Regulatory Action Against the Use of Selective Serotonin Reuptake Inhibitors in Under 18s in the United Kingdom: Ecological Study*, 336 BMJ 515, 516 (2008), *available at* http://www.bmj.com/cgi/content/abstract/bmj. 39462. 375613.BEV1.

[58] Gibbons, *supra* note 51, at 1359; Jon N. Jureidini, Letter to the Editor, *The Black Box Warning: Decreased Prescriptions and Increased Youth Suicide?,* 164 AM. J. PSYCHIATRY 1907 (December 2007) (criticizing the Gibbons' study as flawed and misleading).

[59] WLF/ACEP Brief at 18.

nothing in common with risks inherent in prescription drugs. As the result, public advisory warnings related to any of these things have no relevance to preemption of failure-to-warn claims or arguments that "overwarning" doctors justifies it. *Id.* In fact, even if every failure-to-warn claim were preempted, it would do nothing to prevent another fish "scare" of this sort.

This and the following two examples demonstrate only that well-informed medical professionals are the best defense against public panics. Moreover, it shows that direct-to-consumer medical advice, including the kind contained in self-help books and drug industry advertising, can sometimes be misleading and harmful to patient safety.

Contraceptives and Abortion Rates

Industry *amici* next attempt to illustrate alleged overwarning by highlighting "Dear Doctor" letters issued by British, but not American, health authorities that allegedly caused British women to "suddenly stop taking their [birth control] pills," even though these letters did not advise them to do so, "because they

panicked."[60] Industry *amici* then claim a link to increased abortion rates in Europe.[61]

Preemption will not prevent the filing of the citizen petition that caused FDA to have to consider the matter, even though it took no action.[62] FDA and the drug industry will still have to deal with the same assertions of statutory and First Amendment rights by others that they themselves assert. Preemption will also not cure the patient non-compliance and public panic described nor did either result from pressure from litigation. Finally, unintended pregnancies and resulting abortions have many causes. Lawsuits regarding drug labels are not one of them.

Thimerisol and Measles Vaccine

The final "example" of alleged overwarning and litigation driving drugs from the market is a particularly inappropriate one.[63] Thimerisol is not a

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[60] *Id.* at 22 (quoting L. Dillner, *Pill Scare Linked to a Rise in Abortions*, 312 BMJ 996 (1996)).

[61] WLF/ACEP Brief at 22.

[62] *See id.* at 20; *and* 21 C.F.R. § 10.30 (2008).

[63] National Childhood Vaccine Injury Act of 1986, 42 U.S.C. §§ 300 aa1-34 (2006) (sets up no-fault system for processing vaccine claims).

prescription drug.[64] Instead, it is a preservative used when vaccines are dispensed in multi-dose vials.[65] Moreover, even the sources *amici* cite do not suggest that failure-to-warn claims caused the thimerisol "scare" or led to any measles outbreak. As the result, preemption would do nothing to prevent similar occurrences.

Bendectin and Pregnant Women

PhRMA/BIO claim that the anti-nausea drug Bendectin's removal from the market was the result of a scare initiated by *The National Enquirer* and allegedly unwarranted litigation that arose from it.[66] *The National Enquirer* is not yet a part of FDA nor does it play any role in drafting drug warnings. For these reasons, this is hardly a case of overwarning.

Nor do Bendectin lawsuits provide any justification for preemption. Even PhRMA admits the Bendectin experience is an isolated example.[67]

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[64] *See* U.S. FOOD & DRUG ADMINISTRATION, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, THIMERISOL IN VACCINES, *available at* http://www.fda.gov/Cber/vaccine/thimerosal.htm#t1 (last visited Aug. 12, 2008).

[65] *Id.*; *see also* 21 C.F.R. § 610.15(a) (2005).

[66] PhRMA/BIO Brief at 23.

[67] PhRMA's own spokesman admitted that Bendectin is the only drug ever withdrawn from the market solely because of bad publicity surrounding litigation. Gina Kolata, *Controversial Drug Makes a Comeback,* N.Y. TIMES, Sept. 26, 2000, at F-1.

Moreover, Bendectin is not really gone: its ingredients – vitamin B6 and the antihistamine doxylamine – are sold without a prescription. *Id.* Most important, if, as PhRMA/BIO seems to imply, these claims were scientifically baseless, the solution is not to preempt a whole class of claims entirely, but rather to take the much less draconian approach this Court outlined in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), which arose from Bendectin litigation, addressed the same issues PhRMA/BIO raises here, and established the legal threshold for admitting scientific evidence of causation. While medical *amici* agree that truly frivolous lawsuits do not belong in our legal system, their existence provides no reason to preempt all failure-to-warn claims, even meritorious ones.

Petitioner and its *amici* would have this Court stop the flow to doctors of the kind of critical drug safety information that has been withheld from the medical community in the past based upon the unfounded fear of overwarning in prescription drug labels. Weighing the relative risks of harm, as this Court must do, one commentator concluded:

> To justify the absolute protection from liability for withholding risk information from sophisticated physicians that preemption would provide on the chance that physicians may under-prescribe a dangerous drug requires much stronger

> support than the generalized concern of over-warning currently articulated.[68]

Because Wyeth's *amici* have done little more here than attempt to create the very kind of unwarranted public health panic over alleged overwarning that they purport to foreclose through preemption, this Court should reject "overwarning" as justifying preemption of failure to warn claims.

B. Prescription Drug "Underuse" Is Not Attributable to Failure-to-Warn Claims or Alleged "Overwarning"

To the extent Wyeth's *amici* have failed to demonstrate any overwarning problem in the prescription drug context by providing at least one instance of true overwarning in any prescription drug label, they cannot succeed in blaming the alleged underuse of prescription drug on overwarning. Nevertheless, WLF/ACEP devote an entire section of their brief to the notion that "recent scientific and medical studies confirm the adverse public health consequences of overwarning" and argue that prescription drug underuse is just such a consequence.[69] Even a cursory review of the studies cited reveals, however, that none support the notion

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[68] Davis, *supra* note 26, at 1143.

[69] WLF/ACEP Brief at 13.

that alleged "overwarning" attributable to litigation is any factor in the alleged underuse of prescription drugs. Instead, the cited studies conclude that misperceptions in the public domain or lack of knowledge on the part of physicians, patients, and pharmacists caused the alleged underuse of prescription drugs. In fact, none of the listed studies cite to, quote from, or reference any FDA-approved labeling for any prescription medication, nor do they mention tort claims as a factor in causing underuse.

The Shrank study,[70] for example, found that, while underuse of medications was a significant problem in pharmacologic care, even greater problems were found in "education and documentation" and "appropriate medication monitoring processes." *Id.* Thus, the study says no more than that there are several aspects to the allegedly substandard prescribing practices of physicians in America, one of which is underuse of medications. It says nothing to support the notion that alleged "overwarning" resulting from tort lawsuits is an impediment to the delivery of appropriate pharmacologic care to patients.

While industry *amici* suggest that "medical researchers in peer-reviewed publications repeatedly have pointed to unfounded safety concerns as a driving

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[70] William H. Shrank et al., *The Quality of Pharmacologic Care for Adults in the United States,* 44 MEDICAL CARE 936, 940 (2006).

factor" in drug underutilization,[71] the Gutierrez[72] study does not hint that such misperceptions are the result of overwarning in prescription drug labels. Instead, it observes that "It is not known why ß-Adrenoceptor Antagonists are not universally prescribed enough despite compelling evidence for their use in patients with coronary disease." It then posits that "many have reasoned that physicians . . . are reluctant to give ß-Adrenoceptor Antagonists because of what they perceive as absolute contraindications . . ." *Id.* It does not, however, attribute such perceptions to anything found in a prescription drug label. Instead, the study ascribes alleged underuse to misperceptions or misinformation in physicians' general knowledge base.

WLF/ACEP also cites Wenzel,[73] who focused on ***pharmacists'*** and ***patients'*** knowledge of drug risks and urges patient education. *Id.* at 642. There is nothing in his article to suggest that alleged underutilization of drugs is the result of tort claims or alleged overwarning in prescription drug labels.

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[71] WLF/ACEP Brief at 14-15.

[72] Michael A. Gutierrez et al., *Underutilization of ß-Adrenoceptor Antagonists Post-Myocardial Infarction,* 5 AM. J. CARDIOVASC. DRUGS 23, 27 (2005).

[73] Richard Wenzel, *Migraine Headache Misconceptions: Barriers to Effective Care*, 24 PHARMACOTHERAPY 638, 641 (2004).

Finally, WLF/ACEP cite Koren and Levichek[74] who also conclude that misperceptions and misinformation in the public domain about anti-nausea drug risks in pregnancy is an impediment to its appropriate use.[75] Nothing in their study attributes this confusion to tort litigation or alleged overwarning. Instead, even FDA has admitted that its pregnancy category labeling is outmoded and inadequate. For that reason, it proposed "major revisions" in May 2008, long after the article cited was published, "to provide more complete information about the effects of medicines used during pregnancy and breast-feeding."[76]

In short, Wyeth's *amici* cannot show any connection between alleged overwarning and alleged prescription drug underuse because there is not one.[77] The mere unfounded fear of alleged overwarning and

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[74] Gideon Koren et al., *The Teratogenicity of Drugs for Nausea and Vomiting of Pregnancy: Perceived Versus Real Risk*, 186 AM. J. OBSTET. GYNECOL. 5248, 5252 (2002)

[75] WLF/ACEP Brief at 15.

[76] *See* U.S. FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, PREGNANCY AND LACTATION LABELING (May 28, 2008), *available at* http://www.fda.gov/cder/regulatory/pregnancy_labeling/default. htm.

[77] *See, e.g.*, Michael A. Steinman et al., *Polypharmacy and Prescribing Quality in Older People*, 54 J. AM. GERIATRICS SOC. 1516 (2006) (study concluding that alleged drug under- and overuse occur at similar rates).

resulting underuse of prescription drugs cannot justify preempting all failure-to-warn claims, leaving injured patients in the cold, and doctors in the dark.

CONCLUSION

This brief ends as it began: with the Hippocratic oath. In its spirit, *Amicus,* the California Medical Association, ask that this Court do no harm and affirm the decision of the Vermont Supreme Court.

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